- Opioid analgesics and antagonists
- Treatment of neurodegenerative diseases (Part 1)

Lecture 6

College of Pharmacy

By:

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Opioid analgesics and antagonists

- Pain is defined as **an unpleasant sensation** that can be either **acute** or **chronic** and is **a consequence of complex neurochemical processes in the peripheral and central nervous systems (CNS).**

- For **mild to moderate arthritic pain** (nociceptive pain), non-opioid analgesics such as nonsteroidal anti-inflammatory drugs are often effective.

- **Neuropathic pain** responds best to anticonvulsants, tricyclic antidepressants, or serotonin/norepinephrine reuptake inhibitors.

- However, **severe acute pain or chronic malignant or nonmalignant pain**, **opioids** can be considered as part of the treatment plan in select patients (Figure 1).

- All opioids act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, **endorphins, enkephalins, and dynorphins**).

- Although the opioids have a broad range of effects, their primary use is to relieve intense pain that results from surgery, injury, or chronic disease.

STRONG AGONISTS

Alfentanil ALFENTA
Fentanyl ABSTRAL, ACTIQ, DURAGESIC, FENTORA, IONSYS, LAZANDA, SUBSYS
Heroin GENERIC ONLY
Hydrocodone HYSINGLA, LORTAB*, NORCO*, VICODIN*, ZOHYDRO ER
Hydromorphone DILAUDID, EXALGO
Levorphanol GENERIC ONLY
Meperidine DEMEROL
Methadone DOLOPHINE, METHADOSE
Morphine ARYMO ER, KADIAN, MORPHABOND, MS CONTIN
Oxycodone OXAYDO, OXYCONTIN, PERCOCET*, ROXICODONE
Oxymorphone OPANA
Remifentanil ULTIVA
Sufentanil SUFENTA

MODERATE/LOW AGONISTS

Codeine GENERIC ONLY

MIXED AGONIST–ANTAGONIST AND PARTIAL AGONISTS

Buprenorphine BELBUCA, BUPRENEX, BUTRANS, PROBUPHINE
Butorphanol GENERIC ONLY
Nalbuphine GENERIC ONLY
Pentazocine TALWIN

ANTAGONISTS

Naloxone EVZIO, NARCAN
Naltrexone VIVITROL

OTHER ANALGESICS

Tapentadol NUCYNTA
Tramadol CONZIP, ULTRAM

Figure 1: Summary of opioid analgesics and antagonists with common trade names. *= Contains acetaminophen.

- Opioids are **natural, semisynthetic, or synthetic** compounds that produce morphine-like effects (Figure 2).

- Unfortunately, widespread availability of opioids has led to abuse of agents with euphoric properties.

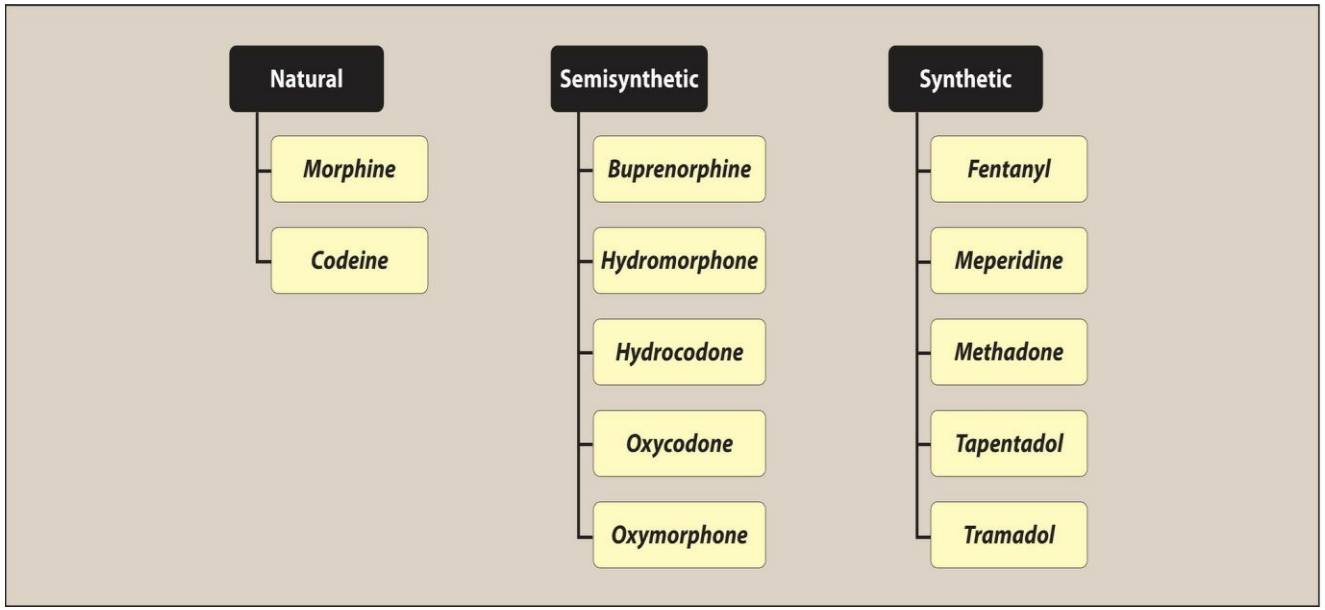

Figure 2: Origin of opioids: natural, semisynthetic, or synthetic

Receptor Subtype	Functions	Endogenous Opioid Peptide Affinity
μ (mu)	Supraspinal and spinal analgesia; sedation; inhibition of respiration; slowed gastrointestinal transit; modulation of hormone and neurotransmitter release	Endorphins > enkephalins > dynorphins
δ (delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	Enkephalins > endorphins and dynorphins
κ (kappa)	Supraspinal and spinal analgesia; psychotomimetic effects; slowed gastrointestinal transit	Dynorphins > > endorphins and enkephalins

Figure 3: Opioid receptor subtypes, their functions, and their endogenous peptide affinities.

- All three opioid receptors are members of the **G protein–coupled receptor** family and **inhibit adenylyl cyclase**. They are also **associated with ion channels, increasing postsynaptic K^+ efflux (hyperpolarization) or reducing presynaptic Ca^{2+} influx**, thus impeding neuronal firing and transmitter release in the spinal dorsal horn (Figure 4).

Opioid Agonists

- **Morphine** is the prototypical **strong μ receptor agonist**. **Codeine** is inherently **less potent** and the prototype of the weak μ opioid agonists.

- Currently available opioids have many differences, such as:

Receptor affinity, pharmacokinetic profiles, available routes of administration, and adverse effect profiles.

- Comparing other available opioids to morphine is helpful in identifying the unique differences to guide the selection of a safe and effective pain management regimen (Figure 5).

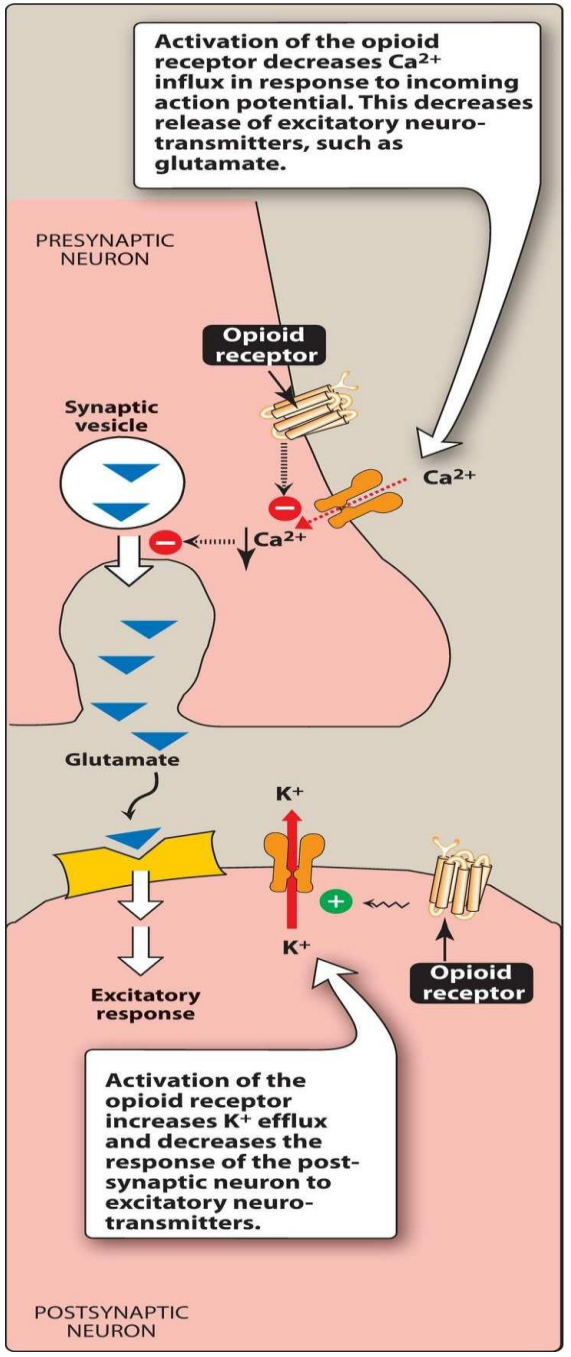

Figure 4: Mechanism of action of μ opioid receptor agonists in the spinal cord.

Opioid	Routes of Administration	Comments
Morphine	PO (IR and ER), PR, IM, IV, SC, IA, SL, EA	• For all drugs listed: opioid class side effects. Metabolism through conjugation in liver and P-glycoprotein. • Active metabolites are renally eliminated and accumulate in renal impairment. • Metabolite M3G has no analgesic action, but can be neuroexcitatory. • Metabolite M6G is two to four times more potent than parent drug; accumulation can cause oversedation and respiratory depression. • Abuse deterrent formulations available.

Methadone	PO, IV, IM, SC	• No active metabolites.
		• Racemic mixture
		  • **Metabolized by many CYP450 isoenzymes:** high risk of drug interactions.
		  • **Substrate of P-glycoprotein**
		• Long and variable half-life increases risk of overdose.
		• Very lipophilic and redistributes to fat stores.
		• Duration of analgesia is much shorter than elimination half-life. Repeated dosing can lead to accumulation.
		• Can prolong QTc interval and cause torsades de pointes.
		• Warning: Conversion to and from *methadone* and other opioids should be done with great care, since equianalgesic dosing varies dramatically.

Fentanyl	IV, EA, IA, TD, OTFC, SL, Buccal, Nasal	• No active metabolites; option for patients with renal dysfunction but should be used with caution. • Metabolized by CYP3A4. • 100 times more potent than *morphine*. • Less histamine release, sedation, and constipation in comparison to *morphine*.
Oxycodone	PO (IR and CR)	• Metabolized by CYP2D6 and CYP3A4. • Black box warning: CYP3A4 drug interactions. • Less histamine release and nausea in comparison to *morphine*. • Abuse-deterrent formulation available.
Oxymorphone	PO (IR and ER), IV	• Immediate release has longer duration of action and elimination half-life (8 hours) compared to other immediate-release opioids. • Oral bioavailability increases with food. • Should be administered 1 to 2 hours after eating. • Bioavailability increased with coadministration of alcohol.

Hydromorphone	PO (IR and ER), PR, IV, SC, EA, IA	• Metabolized via glucuronidation to H6G and H3G which are renally eliminated and can cause CNS side effects in patients with renal insufficiency. • Abuse-deterrent formulation available.
Hydrocodone	PO (IR and ER)	• Active metabolite is *hydromorphone*. • Metabolized by CYP2D6 and CYP3A4. • Abuse-deterrent formulations available.
Tapentadol	PO (IR and ER)	• Centrally acting analgesic; μ agonist activity along with inhibition of norepinephrine reuptake. • Efficacy in treating nociceptive and neuropathic pain. • Metabolized predominately by glucuronidation; no CYP450 interactions. • Seizures and serotonin syndrome can occur in predisposed patients.

Tramadol	PO (IR and ER), Topical	• Metabolized by Phase 1 and 2. CYP2D6, CYP2B6, and CYP3A4 involved in metabolism; watch drug interactions.
		• Serotonin syndrome can occur due to drug interactions.
		• CI for treatment of pain in children <12 years old.
		• CI in children <18 y/o after removal of tonsils/adenoids.
		• Use is not recommended in 12–18 years old who are obese, have severe lung disease, or have sleep apnea
		• Use is not recommended in breastfeeding mothers due to adverse reactions in breastfed infants.
		• Warning:
		  • Renal impairment dosing required.
		  • Review dosing recommendations in severe hepatic impairment.

Codeine	PO, SC	• Prodrug: Metabolized by CYP2D6 to the active drug *morphine*. • Rapid metabolizers of CYP2D6 can experience toxicity. • Inhibitors of CYP2D6 will prevent conversion of *codeine* to *morphine*, thereby preventing pain control. • Do not use in patients with renal dysfunction. • Use only for mild or moderate pain. • CI in treatment of pain or cough in children <12 years old. • CI in children <18 years old after removal of tonsils/adenoids. • Use is not recommended in 12–18 years old who are obese, have severe lung disease, or have sleep apnea. • Use is not recommended in breastfeeding mothers due to adverse reactions in breastfed infants.
Meperidine	PO, IV, SC, EA, IA	• Not recommended as first-line opioid choice. • Active metabolite normeperidine accumulates with renal dysfunction, leading to toxicity. • *Naloxone* does not antagonize the effects of normeperidine; could worsen seizure activity. • Do not use in elderly, patients with renal dysfunction, or for chronic pain management.
Buprenorphine	SL, TD, IM, IV, Buccal (transmucosal), Implant	• Long duration of action; very lipophilic. • Incompletely reversible by *naloxone*. • Metabolized by CYP3A4; watch for drug interactions with strong CYP 3A4 inhibitors or inducers. • Can prolong QTc interval. • Transdermal patch is applied every 7 days. • Abuse-deterrent formulations available.

CI = contraindicated; CR = controlled-release; EA = epidural anesthesia; H3G = hydromorphone-3-glucuronide; H6G = hydromorphone-6-glucuronide; IA = intrathecal anesthesia; IM = intramuscular; IR = immediate release; IV = intravenous; M3G = morphine-3-glucuronide; M6G = morphine-6-glucuronide; OTFC = oral transmucosal fentanyl citrate; PO = orally; PR = rectally; SC = subcutaneous; SL = sublingual; TD = transdermal.
Note: Many different acronyms may be used to indicate a medication is extended-release. Examples include CR (controlled-release), LA (long-acting), ER (extended-release).

Figure 5: Summary of clinically relevant properties for selected opioids.

A. Morphine

Mechanism of action

- Morphine and other opioids exert analgesic effects by **interacting with opioid receptors on the membranes of neuronal cells in the CNS and other anatomic structures**, such as the smooth muscles of the gastrointestinal (GI) tract and the urinary bladder.
- **Morphine** is **somewhat selective to the μ opioid receptor but has some affinity for the κ and δ receptors.**
- Morphine also **inhibits the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli**.

Some therapeutic uses of morphine and other opioids are listed in (Figure 6).

Therapeutic Use	Comments
Analgesia	*Morphine* is the prototype opioid agonist. Opioids are used for pain in trauma, cancer, and other types of severe pain.
Treatment of diarrhea	Opioids decrease the motility and increase the tone of intestinal circular smooth muscle. [Note: Agents commonly used include *diphenoxylate* and *loperamide* (see chapter 40).]
Relief of cough	*Morphine* does suppress the cough reflex, but *codeine* and *dextromethorphan* are more commonly used.
Treatment of acute pulmonary edema	Intravenous *morphine* dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly via the vaso-dilatory effect. This, in effect, decreases cardiac preload and afterload, as well as anxiety experienced by the patient.
Anesthesia	Opioids are used as pre-anesthetic medications, for systemic and spinal anesthesia, and for postoperative analgesia.

Figure 6: Selected clinical uses of opioids.

Actions

a. Analgesia

Morphine and other opioids relieve pain by raising the pain threshold at the spinal cord level and by altering the brain's perception of pain.

b. Euphoria

Morphine produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmental area.

c. Respiration

Morphine causes respiratory depression by reduction of the responsiveness of medullary respiratory center neurons to carbon dioxide. **Respiratory depression is the most common cause of death in acute opioid overdoses**. Tolerance to this effect develops with repeated dosing, which allows for the safer use of morphine for the treatment of pain when the dose is correctly titrated.

d. Depression of cough reflex

Both morphine and codeine have antitussive properties.

e. Miosis

The pinpoint pupil characteristic of morphine use results from stimulation of μ and κ receptors. This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.

f. Emesis

Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting.

g. GI tract

Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. Morphine also increases the tone of the anal sphincter. Morphine and other opioids produce constipation, with little tolerance developing. Morphine can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

h. Cardiovascular

Morphine has no major effects on blood pressure or heart rate at **lower dosages**, but hypotension and bradycardia may occur at **higher doses**. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure. Morphine is usually contraindicated in individuals with head trauma or severe brain injury.

i. Histamine release

Morphine releases histamine from mast cells causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, morphine should be used with caution in patients with asthma.

j. Hormonal actions

Prolonged use of morphine may lead to opioid-induced androgen deficiency due to suppression of the hypothalamic–pituitary–gonadal axis (HPA). This results in decreased production of sex hormones, especially testosterone, resulting in many clinical symptoms (See; figure 7).

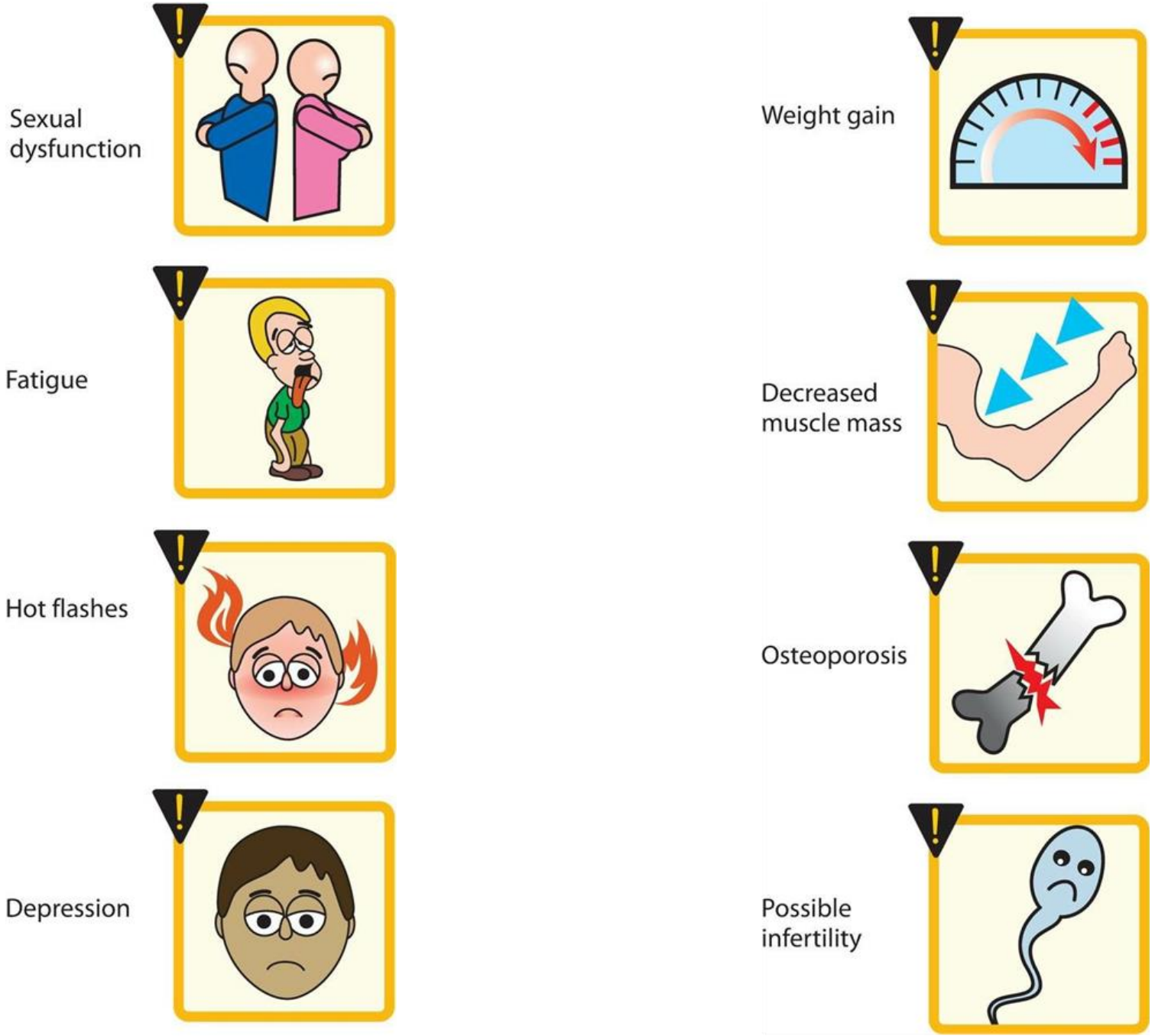

Figure 7: Clinical symptoms associated with opioid-induced androgen deficiency (OPIAD).

k. Labor

Morphine may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

Pharmacokinetics

a. Administration

Absorption of morphine after oral administration is slow and erratic. Extended-release oral preparations provide more consistent plasma levels. SC and IV injections produce the most reliable response.

b. Distribution

Morphine rapidly enters all body tissues, including the fetuses of pregnant women. It should not be used for analgesia during labor. Infants born to addicted mothers show physical dependence on opioids and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of morphine crosses the blood–brain barrier, because morphine is the least lipophilic of the common opioids. By contrast, the more lipid-soluble opioids, such as fentanyl and methadone, readily penetrate the CNS.

c. Fate

Morphine is conjugated with glucuronic acid in the liver to two active metabolites (morphine-6-glucuronide [M6G] and morphine-3-glucuronide [M3G]), which are renally excreted. M6G is a very potent analgesic. M3G does not have analgesic activity but is believed to cause neuroexcitatory effects.

The duration of action of morphine is 4 to 5 hours when administered systemically to opioid-naïve individuals but considerably longer when injected epidurally because the low lipophilicity prevents redistribution from the epidural space.

Adverse effects

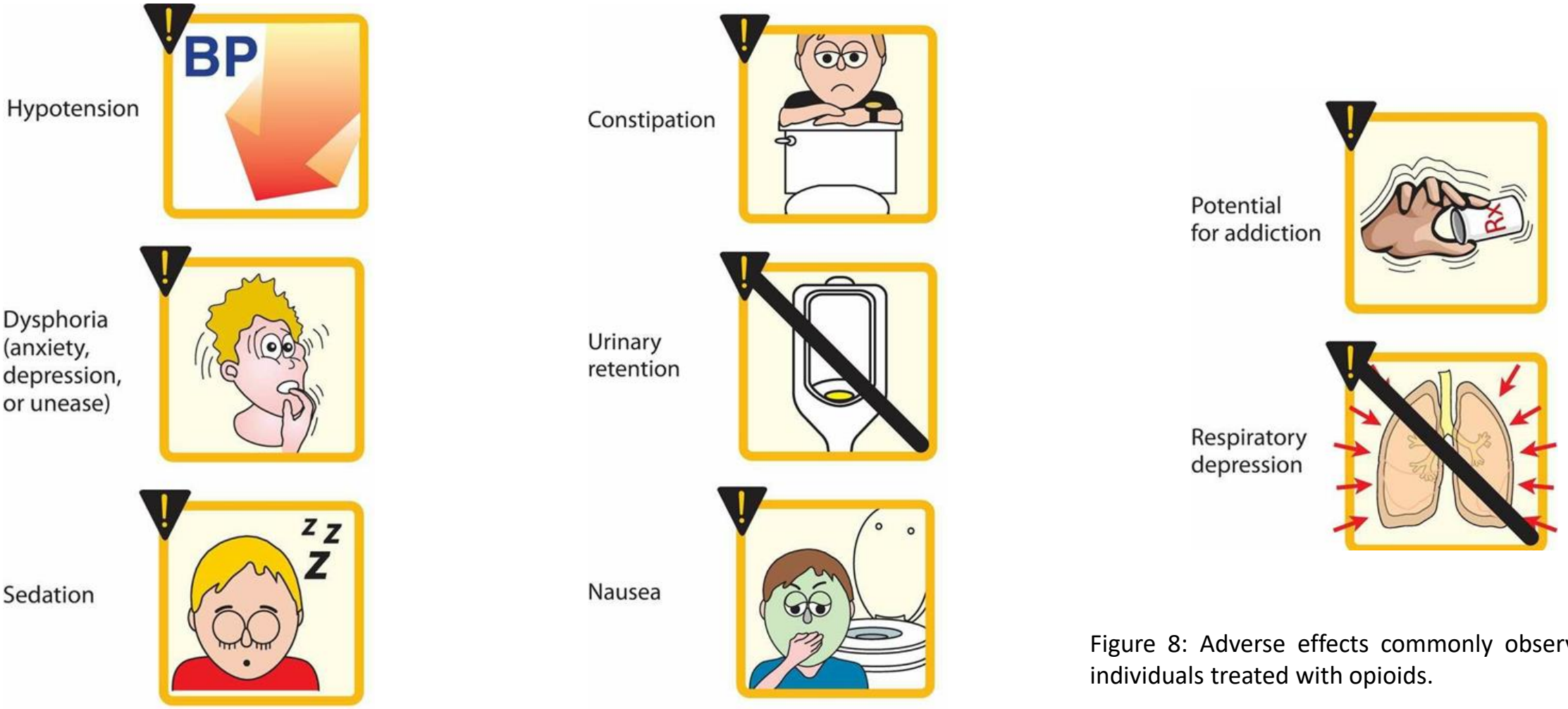

Figure 8: Adverse effects commonly observed in individuals treated with opioids.

Tolerance and physical dependence

- Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, emetic, and sedative effects of morphine.
- Tolerance usually does not develop to miosis or constipation.
- Physical and psychological dependence can occur with morphine and other agonists.
- Withdrawal produces a series of autonomic, motor, and psychological responses that can be severe, although it is rare that withdrawal effects cause death.

Drug interactions

- Drug interactions with morphine are possible. The depressant actions of morphine are enhanced by coadministration with CNS depressant medications such as phenothiazines, monoamine oxidase inhibitors (MAOIs), and benzodiazepines.
- A black box warning also has been included on the labeling of both opioids and benzodiazepines to alert prescribers of this dangerous combination.

B. Codeine

Codeine is a naturally occurring opioid and a weak analgesic compared to morphine. It is used for mild to moderate pain. The analgesic actions of codeine are derived from its conversion to morphine by the CYP2D6 enzyme.

C. Oxymorphone and Oxycodone

Oxymorphone and oxycodone are orally active, semisynthetic analogs of morphine and codeine, respectively.

D. Hydromorphone and hydrocodone

They are orally active, semisynthetic analogs of morphine and codeine, respectively.

E. Fentanyl

Fentanyl is a synthetic opioid chemically related to meperidine. Fentanyl has 100-fold the analgesic potency of morphine and is used for anesthesia and acute pain management. The drug is highly lipophilic and has a rapid onset and short duration of action (15 to 30 minutes). It is usually administered IV, epidurally, or intrathecally.

F. Sufentanil, alfentanil, remifentanil, and carfentanil

They are synthetic opioid agonists related to fentanyl. These agents differ in potency and metabolic disposition.

G. Methadone

Methadone is a synthetic, orally effective opioid that has variable equianalgesic potency compared to that of morphine, and the conversion between the two products is not linear. Methadone is a μ agonist, an antagonist of the N-methyl-D-aspartate (NMDA) receptor, and a norepinephrine and serotonin reuptake inhibitor. Therefore, it is useful in the treatment of both nociceptive and neuropathic pain.

H. Meperidine

Meperidine is a lower-potency synthetic opioid structurally unrelated to morphine. It is used for acute pain and acts primarily as a κ agonist, with some μ agonist activity.

Partial Agonists and Mixed Agonist–Antagonists

- Partial agonists bind to the opioid receptor, but they have less intrinsic activity than full agonists.
- Drugs that stimulate one receptor but block another are termed mixed agonist–antagonists.
- The effects of these drugs depend on previous exposure to opioids; individuals who are opioid-naïve, mixed agonist–antagonists show agonist activity and are used to relieve pain. However, In the presence of a full agonist, the agonist–antagonist drugs may precipitate opioid withdrawal symptoms.

A. Buprenorphine

- It acts as a potent partial agonist at the μ receptor and an antagonist at the κ receptors.
- It is very lipophilic and has a longer duration of action.
- Due to high affinity for the mu receptor, buprenorphine can displace full μ agonists, leading to withdrawal symptoms in an opioid-dependent patient.
- Because of the partial μ agonist activity, buprenorphine provides a **“ceiling effect,”** causing less euphoric effects and a lower abuse potential than that of full agonists.
- Additionally, the risk of opioid-induced respiratory depression may be lower when compared with full agonists, except when combined with CNS depressants such as benzodiazepines.
- Buprenorphine is available in sublingual, transmucosal, buccal, parenteral, subdermal, and transdermal formulations.
- The drug is approved for moderate to severe pain.

- It has been shown to have shorter and less severe withdrawal symptoms compared to methadone (Figure 9).
- Adverse effects include:
- Respiratory depression that cannot easily be reversed by naloxone, decreased (or, rarely, increased) blood pressure, nausea, dizziness; and prolongation of the QTc interval.
- Risk factors to evaluate when considering buprenorphine include cardiovascular factors and concurrent drugs that may prolong.

B. Pentazocine

- Pentazocine acts as an agonist on κ receptors and is a weak antagonist or partial agonist at μ receptors.
- It can be administered either orally or parenterally.
- It produces less euphoria compared to morphine, but in higher doses, respiratory depression, increased blood pressure, tachycardia, and hallucinations can occur, thus, it is rarely used for management of pain.
- Despite its antagonist action, it does not antagonize the respiratory depression of morphine, but it can precipitate withdrawal effects in a morphine user.
- It should be used with caution in patients with angina or coronary artery disease, since it can increase blood pressure.

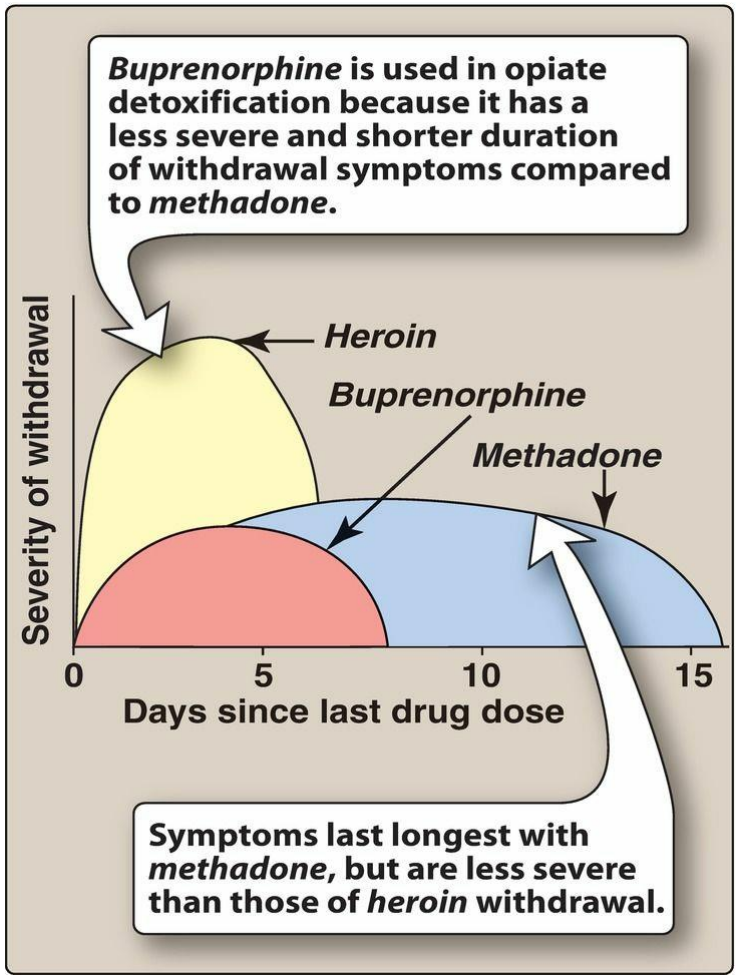

Figure 9: Severity of opioid withdrawal symptoms after abrupt withdrawal of equivalent doses of heroin, buprenorphine, and methadone.

C. Nalbuphine and butorphanol

- They are mixed opioid agonist–antagonists. Like pentazocine, they play a limited role in the treatment of chronic pain.
- Butorphanol is available in a nasal spray that has been used for severe headaches, but it has been associated with abuse. Both products are available in an injectable formulation.
- Their propensity to cause psychotomimetic effects is less than that of pentazocine.
- In contrast to pentazocine and butorphanol, nalbuphine does not affect the heart or increase blood pressure.
- A benefit of all three medications is that they exhibit a ceiling effect for respiratory depression.

Other Analgesics

A. Tapentadol

- Tapentadol, a centrally acting analgesic, is an agonist at the μ opioid receptor and an inhibitor of norepinephrine reuptake.
- It is used to manage moderate to severe acute and chronic pain, including neuropathic pain associated with diabetic peripheral neuropathy.
- It is mainly metabolized to inactive metabolites via glucuronidation, and it does not inhibit or induce the CYP450 enzyme system; and because it does not produce active metabolites, dosing adjustment is not necessary in mild to moderate renal impairment.

- It should be avoided in patients who have received MAOIs within the past 14 days.
- It is available in an immediate-release and extended-release formulation.

B. Tramadol

- Tramadol is a centrally acting analgesic that binds to the μ opioid receptor.
- It undergoes extensive metabolism via CYP2D6, leading to an active metabolite, which has a much higher affinity for the mu receptor than the parent compound.
- It weakly inhibits reuptake of norepinephrine and serotonin.
- It is used to manage moderate to severe pain.
- It has less respiratory-depressant activity compared to morphine.
- Administration of naloxone can only partially reverse tramadol toxicity and has been associated with an increased risk of seizures.
- Overdose or drug–drug interactions with SSRIs, MAOIs, and tricyclic antidepressants can lead to toxicity manifested by CNS excitation and seizures.
- It should be used with caution in patients with a history of seizures.
- As with other agents that bind the μ opioid receptor, tramadol has been associated with misuse and abuse.

Antagonists

- The opioid antagonists bind with high affinity to opioid receptors, but **they fail to activate the receptor-mediated response**.
- Administration of opioid antagonists produces **no profound effects in individuals not taking opioids**.
- In **opioid-dependent patients, antagonists rapidly reverse the effect of agonists,** such as morphine or any full μ agonist, and **precipitate the symptoms of opioid withdrawal**.

Figure 10 summarizes some signs and symptoms of opioid withdrawal.

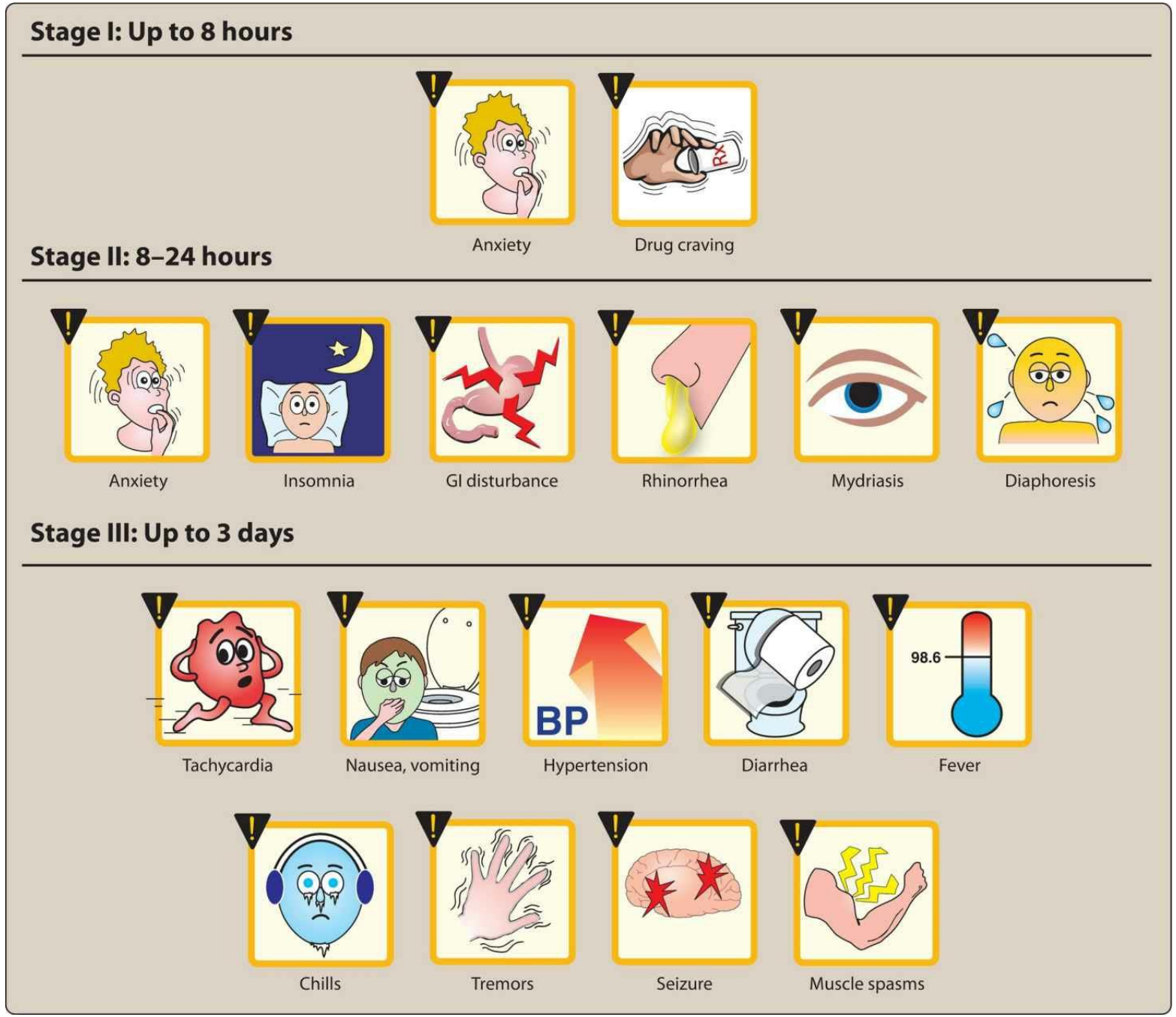

Figure 10: Opiate withdrawal syndrome. GI = gastrointestinal.

A. Naloxone

- Naloxone is a **competitive antagonist at μ, κ, and δ receptors,** with a 10-fold higher affinity for mu than for kappa receptors.
- It rapidly displaces all receptor-bound opioid molecules and, therefore, can reverse the effects of morphine overdose, such as respiratory depression and coma within 1 to 2 minutes of IV administration.
- Naloxone can also be administered intramuscularly, subcutaneously, and intranasally, with a slightly longer onset of 2 to 5 minutes; however, little to no clinical effect is seen with oral naloxone due to extensive first-pass metabolism.
- Since naloxone has a half-life of 30 to 81 minutes, a patient who has been treated for an overdose and recovered may lapse back into respiratory depression, depending on the opioid ingested and dosage form of that opioid.
- Naloxone is available in an autoinjector and a nasal inhaler for community distribution for treatment of opioid overdose involving heroin or prescription opioids.

B. Naltrexone

- Naltrexone has actions similar to those of naloxone, but it has a longer duration of action and can be given orally. For example, a single oral dose of naltrexone blocks the effect of injected heroin for up to 24 hours, and the intramuscular formulation blocks the effect for 30 days.
- Naltrexone in combination with clonidine (and, sometimes, with buprenorphine) is used for rapid opioid detoxification.
- Naltrexone has been reported to cause hepatotoxicity and monitoring of hepatic function is recommended.

Treatment of neurodegenerative diseases

- Neurodegenerative diseases of the CNS include **Parkinson disease, Alzheimer disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS).** These devastating illnesses are characterized by:

The **progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both**.

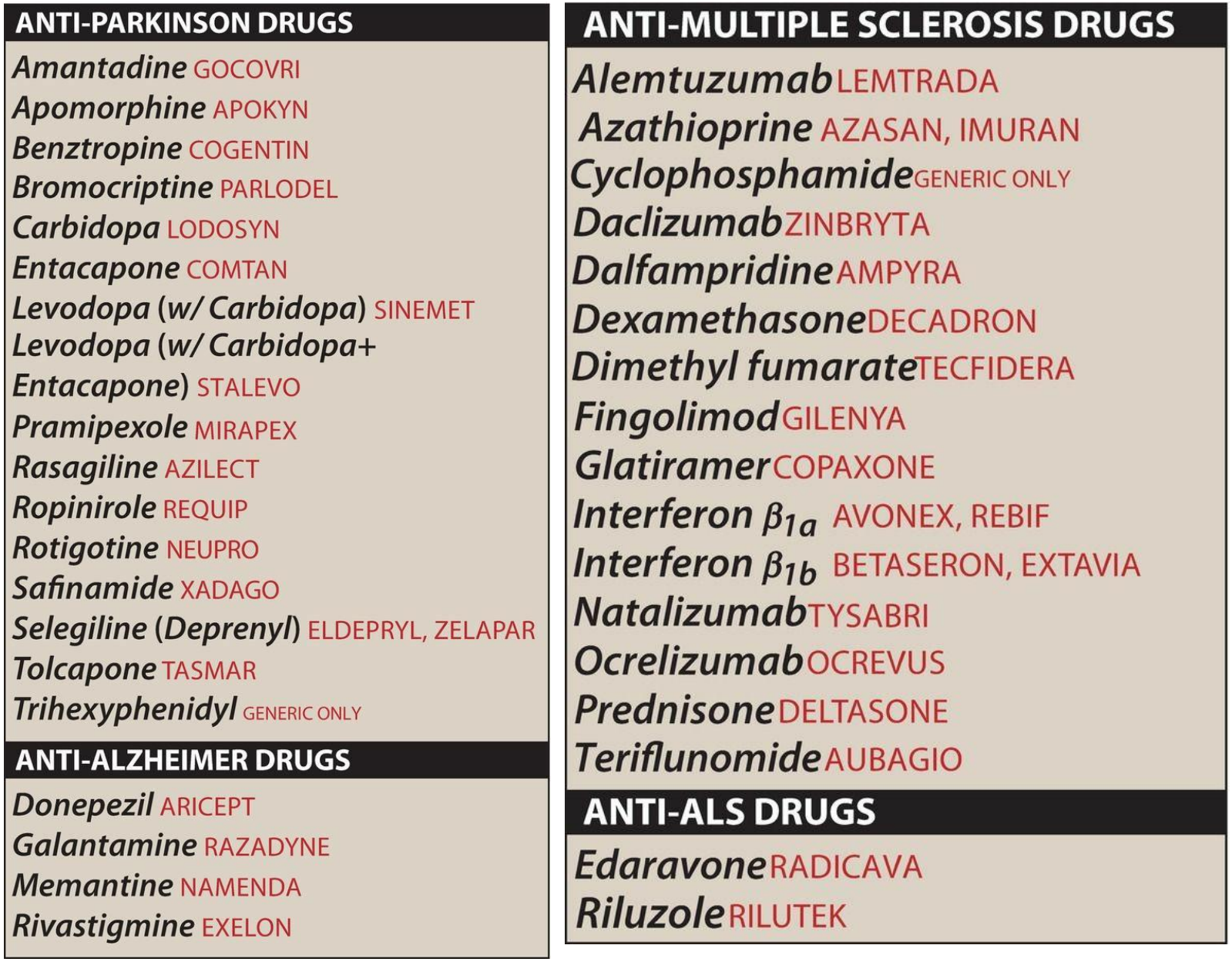

Figure 11: Summary of agents used in the treatment of Neurodegenerative Diseases

Overview of Parkinson Disease

- Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia, and postural and gait abnormalities.
- Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals.
- The cause of Parkinson disease is unknown for most patients. The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the basal ganglia system that are involved in motor control.

- Secondary parkinsonism

Drugs such as the **phenothiazines and haloperidol**, whose major pharmacologic action is blockade of dopamine receptors in the brain, may produce parkinsonian symptoms (also called pseudoparkinsonism). These drugs should **be used with caution in patients with Parkinson disease**.

Strategy of treatment

Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance.

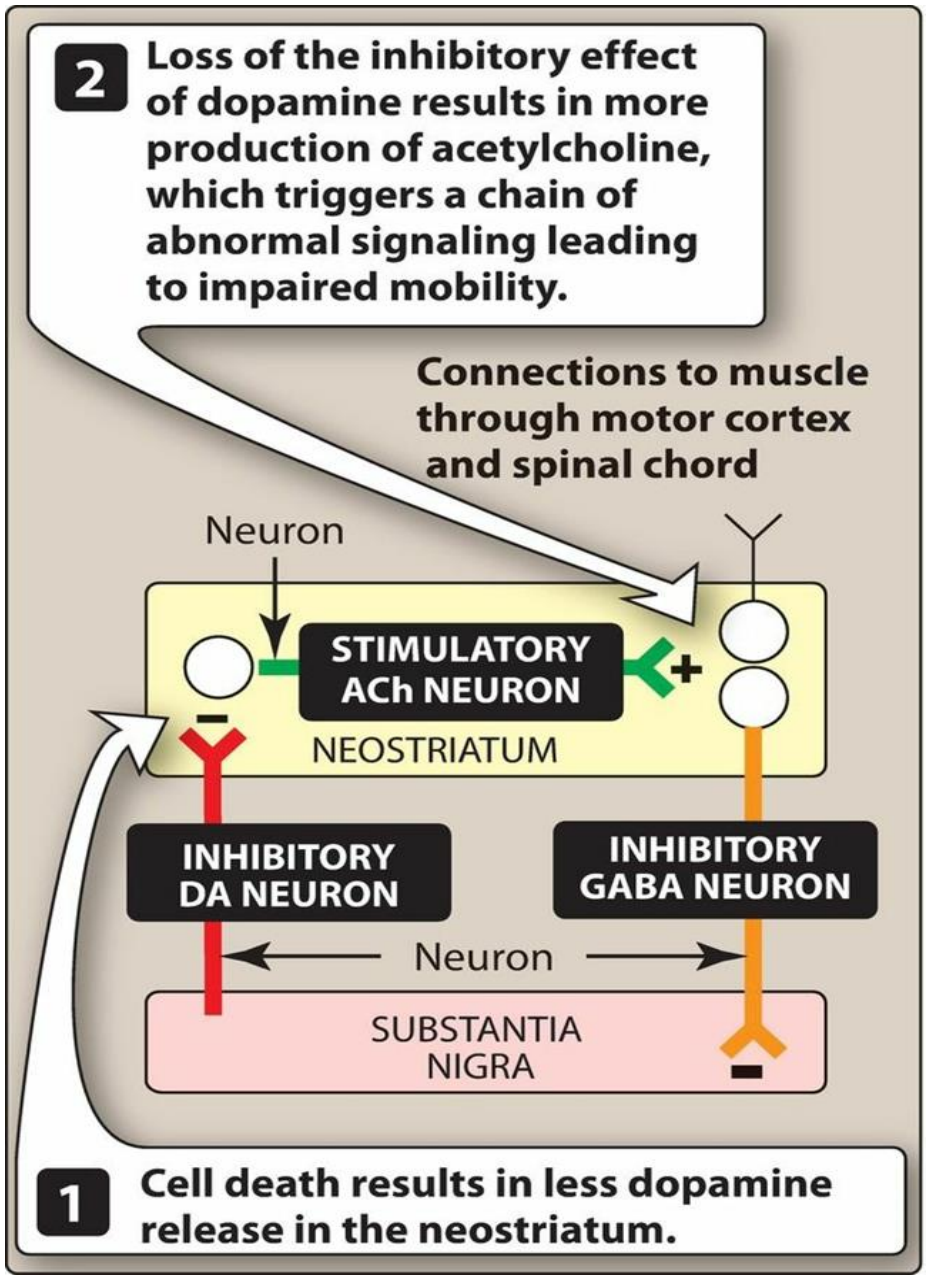

Figure 12: Role of substantia nigra in Parkinson disease. ACh = acetylcholine; DA = dopamine; GABA = γ-aminobutyric acid.

Drugs Used in Parkinson Disease

A. Levodopa and carbidopa

- Levodopa is a metabolic precursor of dopamine (Figure 13). It restores dopaminergic neurotransmission in the neostriatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra.
- In early disease, the number of residual dopaminergic neurons in the substantia nigra is adequate for conversion of levodopa to dopamine.
- Thus, in new patients, the therapeutic response to levodopa is consistent.
- Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of converting exogenously administered levodopa to dopamine. Consequently, motor control fluctuation develops.
- Relief provided by levodopa is only symptomatic, and it lasts only while the drug is present in the body.

Mechanism of action

- Dopamine does not cross the blood–brain barrier, but its immediate precursor, levodopa, is actively transported into the CNS and converted to dopamine (Figure 13).
- Levodopa must be administered with carbidopa (a dopamine decarboxylase inhibitor, diminishes the metabolism of levodopa in the periphery, thereby increasing the availability of levodopa to the CNS).
- Without carbidopa, much of the drug is decarboxylated to dopamine in the periphery, resulting in diminished effect, nausea, vomiting, cardiac arrhythmias, and hypotension. consequently, decreases the severity of adverse effects arising from peripherally formed dopamine.

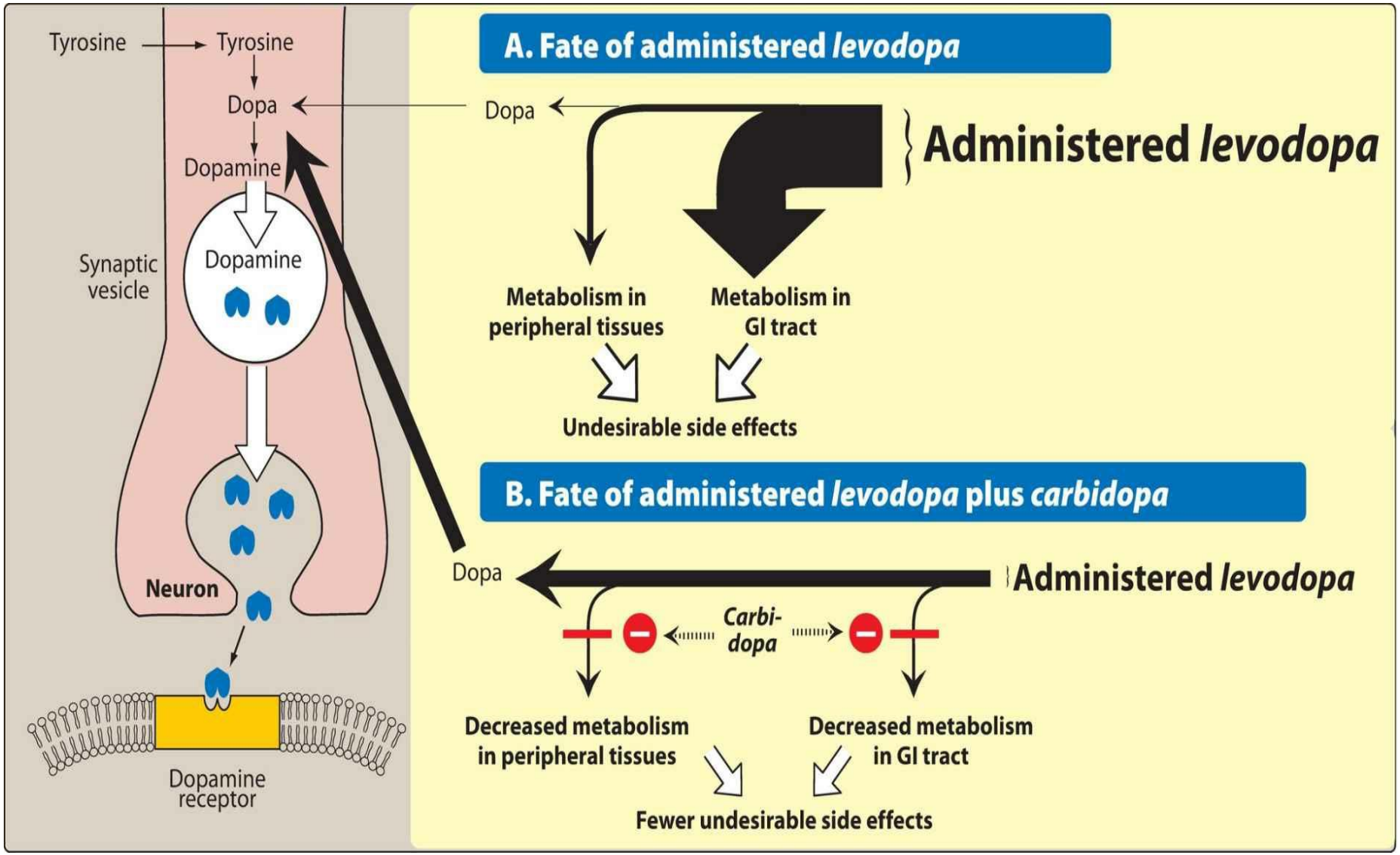

Figure 13: Synthesis of dopamine from levodopa in the absence and presence of carbidopa, an inhibitor of dopamine decarboxylase in the peripheral tissues. (GI = gastrointestinal.)

Therapeutic uses

Treatment of Parkinson disease, it decreases rigidity, tremors, and other symptoms of parkinsonism. Withdrawal from the drug must be gradual.

Absorption and metabolism

- The drug is absorbed rapidly from the small intestine (when empty of food).
- Levodopa has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration.
- This may produce fluctuations in motor response; and motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility.
- Ingestion of meals, particularly if high in protein, interferes with the transport of levodopa into the CNS. Thus, levodopa should be taken on an empty stomach, typically 30 minutes before a meal.

Adverse effects

a. Peripheral effects

- Anorexia, nausea, vomiting, tachycardia, hypotension; adrenergic action on the iris causes mydriasis.
- Saliva and urine may turn brownish color because of the melanin pigment produced from catecholamine oxidation.

b. CNS effects

- Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur.
- These effects are the opposite of parkinsonian symptoms and reflect over activity of dopamine in the basal ganglia.
- Levodopa can also cause mood changes, depression, psychosis, and anxiety.

Interactions

- The vitamin pyridoxine (B6) increases the peripheral breakdown of levodopa and diminishes its effectiveness.
- Concomitant administration of levodopa and nonselective monoamine oxidase inhibitors (MAOIs) can produce a hypertensive crisis caused by enhanced catecholamine production.
- Cardiac patients should be carefully monitored for the possible development of arrhythmias.
- Antipsychotic drugs are generally contraindicated in Parkinson disease.
- However, low doses of atypical antipsychotics, such as quetiapine or clozapine, are sometimes used to treat levodopa-induced psychotic symptoms.

B. Selegiline, rasagiline, and safinamide

- Selegiline, also called deprenyl, selectively inhibits monoamine oxidase (MAO) type B, the enzyme that metabolizes dopamine.
- It does not inhibit MAO type A (metabolizes norepinephrine and serotonin) unless given above recommended doses, where it loses its selectivity.
- By decreasing the metabolism of dopamine, selegiline increases dopamine levels in the brain.
- Unlike nonselective MAOIs, selegiline at recommended doses has little potential for causing hypertensive crises.
- However, the drug loses selectivity at high doses, and there is a risk for severe hypertension.
- Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than mid-afternoon.
- Rasagiline, an irreversible and selective inhibitor of brain MAO type B, has five times the potency of selegiline.
- Unlike selegiline, rasagiline is not metabolized to an amphetamine-like substance.
- Safinamide is also a selective inhibitor of MAO type B indicated for use as an adjunct to levodopa–carbidopa.

C. Catechol-O-methyltransferase inhibitors

- Normally, the methylation of levodopa by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for levodopa metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-O-methyldopa is formed that competes with levodopa for active transport into the CNS (Figure 14).
- Entacapone and tolcapone selectively and reversibly inhibit COMT. Inhibition of COMT by these agents leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine.

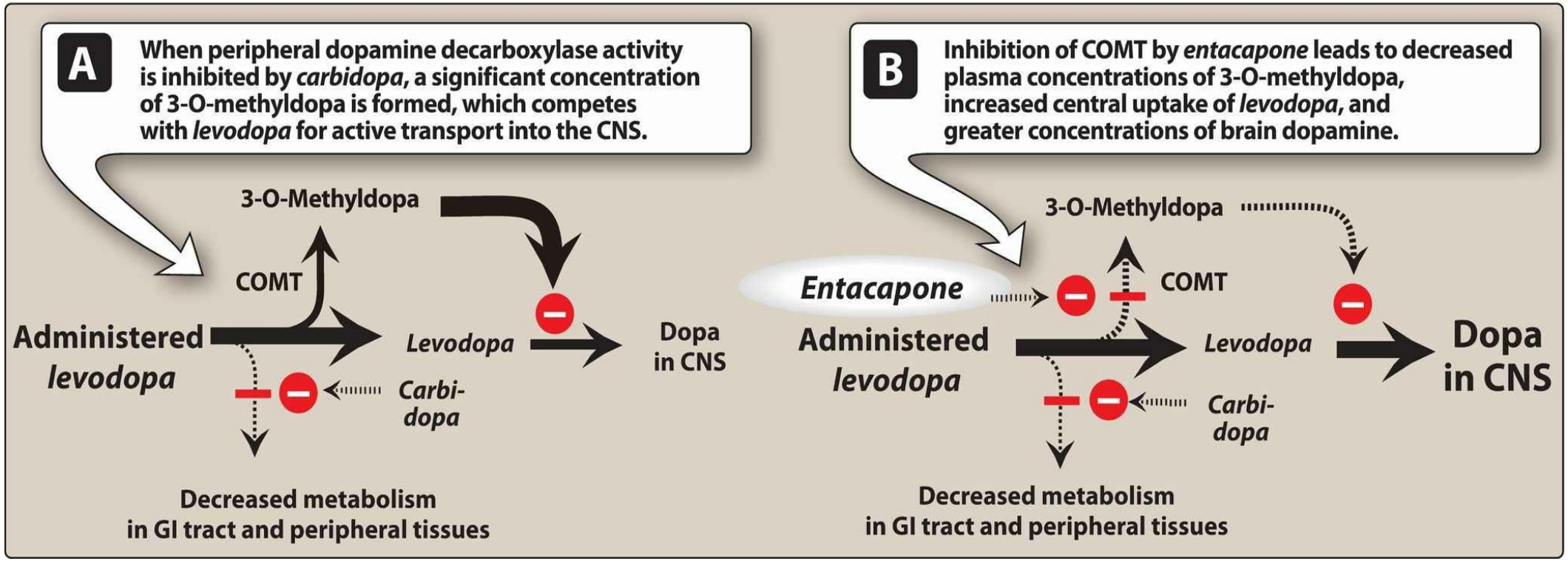

Figure 14: Effect of entacapone on dopa concentration in the central nervous system (CNS). COMT = catechol-O-methyltransferase.

1. Pharmacokinetics

- Oral absorption of both drugs occurs readily and is not influenced by food.
- Tolcapone has a relatively long duration of action compared to entacapone, which requires more frequent dosing.
- Both drugs are extensively metabolized and eliminated in feces and urine.
- The dosage may need to be adjusted in patients with moderate or severe cirrhosis.

2. Adverse effects

Diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, and sleep disorders. Most seriously, fulminating hepatic necrosis is associated with tolcapone use. Entacapone does not exhibit this toxicity and has largely replaced tolcapone in clinical practice.

D. Dopamine receptor agonists

- This group of antiparkinsonian compounds includes bromocriptine, an ergot derivative, and the non-ergot drugs, ropinirole, pramipexole, rotigotine, and apomorphine.
- These agents have a longer duration of action than that of levodopa and are effective in patients exhibiting fluctuations in response to levodopa.

- Initial therapy with these drugs is associated with less risk of developing dyskinesias and motor fluctuations as compared to patients started on levodopa.
- Apomorphine is an injectable dopamine agonist that is used in severe and advanced stages of the disease to supplement oral medications. Adverse effects severely limit the utility of the dopamine agonists (Figure 15).
- Bromocriptine should be used with caution inpatients with a history of myocardial infarction or peripheral vascular disease due to the risk of vasospasm. It also has the potential to cause pulmonary and retroperitoneal fibrosis.
- Unlike the ergotamine derivatives, non-ergot dopamine agonists do not exacerbate peripheral vascular disorders or cause fibrosis.

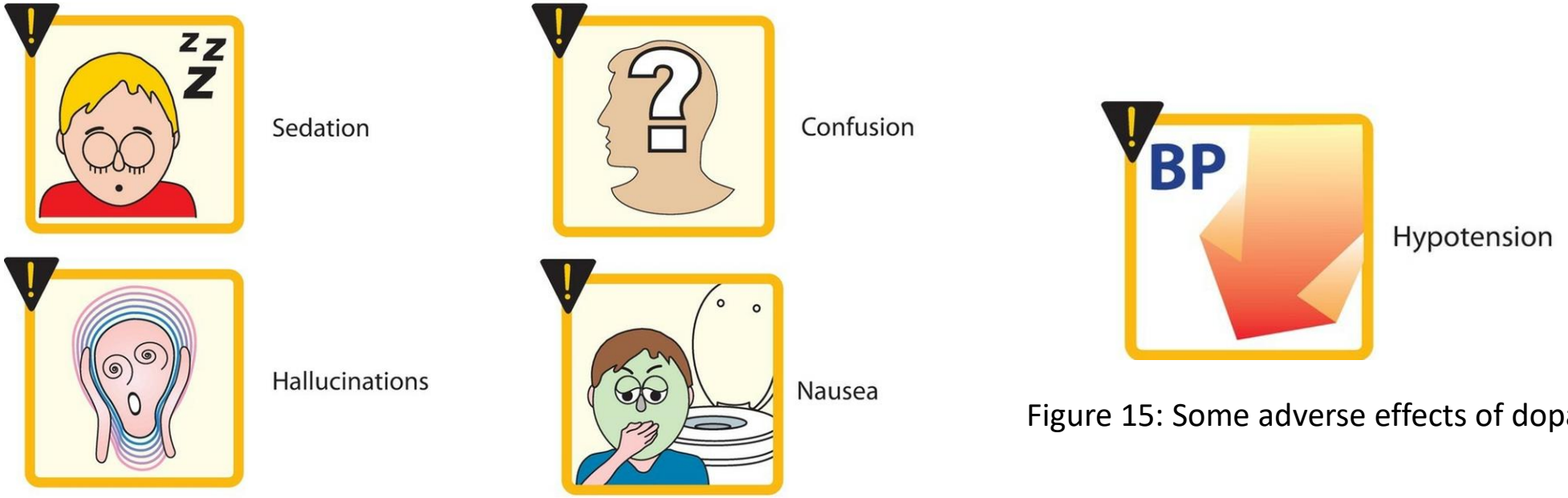

Figure 15: Some adverse effects of dopamine agonists.

Characteristic	*Pramipexole*	*Ropinirole*	*Rotigotine*
Bioavailability	>90%	55%	45%
V_d	7 L/kg	7.5 L/kg	84 L/kg
Half-life	8 h[1]	6 h	7 h[3]
Metabolism	Negligible	Extensive	Extensive
Elimination	Renal	Renal[2]	Renal[2]

Figure 16: Pharmacokinetic properties of dopamine agonists pramipexole, ropinirole, and rotigotine. Vd = volume of distribution. 1* Increases to 12 hours in patients older than 65 years. 2 * Less than 10% excreted unchanged. 3 * Administered as a once-daily transdermal patch.

E. Amantadine

- It was accidentally discovered that the antiviral drug amantadine has an antiparkinsonian action.
- It has several effects such as increasing the release of dopamine, blocking cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate receptors.
- The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur.

F. Antimuscarinic agents

- The antimuscarinic agents are much less efficacious than levodopa and play only an adjuvant role in antiparkinsonism therapy.
- The actions of benztropine and trihexyphenidyl are similar, although individual patients may respond more favorably to one drug or the other.
- Blockade of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission, since it helps to correct the imbalance in the dopamine/acetylcholine activity.
- These agents can induce mood changes and confusion, and produce xerostomia, constipation, and visual problems typical of muscarinic blockers.
- They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.


Thank You!